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| APPLICATION NO.  | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|--|-------------|----------------------|---------------------|------------------|
| 09/639,273   | 08/15/2000  | Michael A. Innis     | 991.001             | 1822             |
| 27476  | 7590        | 03/05/2004           | EXAMINER            |                  |
| Chiron Corporation<br>Intellectual Property - R440<br>P.O. Box 8097<br>Emeryville, CA 94662-8097 |             |                      | ROMEO, DAVID S      |                  |
|  |             |                      | ART UNIT            | PAPER NUMBER     |
|  |             |                      | 1647                |                  |

DATE MAILED: 03/05/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

|                              |                 |              |
|------------------------------|-----------------|--------------|
| <b>Office Action Summary</b> | Application No. | Applicant(s) |
|                              | 09/639,273      | INNIS ET AL. |
|                              | Examiner        | Art Unit     |
|                              | David S Romeo   | 1647         |

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --  
**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

#### Status

- 1) Responsive to communication(s) filed on 07 November 2003.
- 2a) This action is FINAL.                    2b) This action is non-final.
- 3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

#### Disposition of Claims

- 4) Claim(s) 7 and 12-14 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) Claim(s) \_\_\_\_\_ is/are allowed.
- 6) Claim(s) 7 and 12-14 is/are rejected.
- 7) Claim(s) \_\_\_\_\_ is/are objected to.
- 8) Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

#### Application Papers

- 9) The specification is objected to by the Examiner.
- 10) The drawing(s) filed on \_\_\_\_\_ is/are: a) accepted or b) objected to by the Examiner.  
 Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
 Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

#### Priority under 35 U.S.C. § 119

- 12) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
  - a) All    b) Some \* c) None of:
    1. Certified copies of the priority documents have been received.
    2. Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
    3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

#### Attachment(s)

- |   |   |
|---|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)   | 4) <input type="checkbox"/> Interview Summary (PTO-413)                     |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)                                    | Paper No(s)/Mail Date. _____  |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)<br>Paper No(s)/Mail Date _____. | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
|   | 6) <input type="checkbox"/> Other: _____.                                   |

**DETAILED ACTION**

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 08/07/2003 has been entered.

Claims 7, 12-14 are pending and being examined.

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***Claim Rejections - 35 USC § 102***

Claims 7, 12-14 are rejected under 35 U.S.C. 102(b) as being anticipated by Nordfang (v12). The grounds of this rejection are of record. See the Office action mailed 10/21/2002 at pages 3-4. In addition, the examiner relies upon Pedersen (U) and Wun (V). Accordingly, claims 7, 12-14 are rejected under 35 U.S.C. 102(b) as being anticipated by Nordfang (v12), as evidenced by Pedersen (U) and Wun (V).

Norfdang indicates that the recombinant TFPI was purified using the method of Pedersen (U). See Norfdang, page 10371, right column, full paragraph 1. Pedersen (U) teaches that the recombinant TFPI was purified to homogeneity. See Pedersen (U), page 16786, paragraph bridging left and right columns. The fact that the recombinant TFPI was purified to homogeneity indicates that it is "free of mammalian proteins." Pedersen (U) references Wun (V) for the cDNA and amino acid sequence of TFPI. See Pedersen (U), paragraph bridging pages 16786-16787. The N-terminal amino acid sequence of

Pedersen's TFPI is SEQ ID NO: 7, as evidenced by Wun (V). See Wun (V), Abstract and Figure 2.

**New Formal Matters, Objections, and/or Rejections:**

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***Claim Rejections - 35 USC § 102***

Claims 7, 12-14 are rejected under 35 U.S.C. 102(b) as being anticipated by Petersen (u7). The grounds of this rejection are of record in the Office action mailed 03/27/2002 at page 3. In addition, the examiner relies upon Wun (V). Accordingly, claims 7, 12-14 are rejected under 35 U.S.C. 102(b) as being anticipated by Petersen (u7),  
10 as evidenced by Wun (V).

The fact that Petersen's TFPI was produced in yeast indicates that it is "free of mammalian proteins."

The phrase "has an inhibitory concentration of at least 1 µg/ml" is ambiguous because it is unclear if the inhibitory concentration is less than or equal to 1 µg/ml, if the  
15 inhibitory concentration is greater than or equal to 1 µg/ml, or if some inhibition is present at 1 µg/ml with inhibition occurring at concentrations above and below 1 µg/ml. Petersen indicates that the TFPI from yeast showed 5-8 times lower anti-coagulant activity than intact TFPI from transfected BHK cells (page 13350, left column, last full paragraph). Petersen also indicates that with full-length TFPI from transfected BHK cells  
20 a concentration of only 0.5 µg/ml was required for 90% inhibition of anti-coagulant activity (page 13349, left column, full paragraph 2). This indicates that the TFPI from yeast has an inhibitory concentration that is greater than or equal to 1 µg/ml or that some inhibition would be present at 1 µg/ml.

Petersen also indicates that the TFPI from yeast transformants seemed to be full-length (page 13350, left column, full paragraph 3). Peterson references Wun (V) for the cDNA and amino acid sequence of TFPI. See Petersen, page 13345, right column, full paragraph 4. The N-terminal amino acid sequence of Petersen's TFPI from yeast  
5 transformants is SEQ ID NO: 7, as evidenced by Wun (V). See Wun (V), Abstract and Figure 2.

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all  
10 obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the  
15 invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 7, 12-14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Petersen (u7), as evidenced by Wun (V), in view of Cousens (A).

The teachings of Petersen are of record in the Office action mailed 03/27/2002 at  
20 page 3.

The fact that Petersen's TFPI was produced in yeast indicates that it is "free of mammalian proteins."

Petersen also teaches that irrespective of promoter or signal, only very low levels of TFPI activity were measure extracellularly with E18 transformants. The YNG452  
25 yeast strain showed a somewhat better ability to secrete active TFPI. However, expression was still fairly low. Page 13345, right column, full paragraph 5. The yeast expression plasmids were designed to produce TFPI with the correct N-terminal

sequence, as indicated in Figure 1. Peterson references Wun (V) for the cDNA and amino acid sequence of TFPI. See Petersen, page 13345, right column, full paragraph 4. The N-terminal amino acid sequence of Petersen's TFPI from yeast transformants is SEQ ID NO: 7, as evidenced by Wun. See Wun (V), Abstract and Figure 2.

5 Petersen does not disclose the production of TFPI in high yield.

Cousens discloses that in many situations, for reasons which have not been resolved, heterologous products, despite active promoters and high copy number plasmids, are produced in only minor amount, if at all, in a microorganism host (column 1, full paragraph 2). Cousens provides methods and compositions for producing 10 heterologous polypeptides in high yield in a eukaryotic or prokaryotic microorganism host, whereby a completely heterologous fused, product is expressed, one part of the peptide being a product shown to be expressed independently in high yield in such host and the remaining part of the product being a polypeptide of interest, resulting in production of the fused product in high yield. Sequences coding for the two polypeptides 15 are fused in open reading frame, where the high yield polypeptide encoding sequence may be at either the 5'- or 3'-terminus. The two polypeptides contained in the expression product may be joined by a selectively cleavable link, so that the two polypeptides may be separated to provide for high yield of each of the polypeptides. Alternatively, the cleavage site may be absent if cleavage of the fused protein is not required for its 20 intended use. Particularly, a yeast host is employed where the high yield polypeptide is superoxide dismutase (SOD). Paragraph bridging columns 1-2. The two polypeptides are a stabilizing polypeptide and a polypeptide of interest (paragraph bridging columns 2-3; column 3, full paragraph 5). To cleave the two polypeptides peptidases can be

employed which are specific for particular sequences of amino acids, such as those peptidases which are involved in the selective cleavage of secretory leader signals from a polypeptide. These enzymes are specific for such sequences which are found with  $\alpha$ -factor and killer toxin in yeast, such as KEX 2 endopeptidase with specificity for pairs of basic residues (paragraph bridging columns 3-4).

Cousens does not teach the production of TFPI in yeast in the sense that Cousens does not anticipate the present claims.

However, it would have been obvious to one of ordinary skill in the art at the time of Applicants' invention to produce TFPI in yeast in low yield, as taught by Petersen, and to modify that teaching, by producing TFPI in yeast in high yield, as taught by Cousens, with a reasonable expectation of success. One of ordinary skill in the art would be motivated to make this modification in order to produce TFPI in high yield.

Where the claimed and prior art products are identical or substantially identical in structure or composition, or are produced by identical or substantially identical processes, a *prima facie* case of either anticipation or obviousness has been established.

The invention is *prima facie* obvious over the prior art.

#### ***Claim Rejections - 35 USC § 112***

Claims 7, 12-14 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The phrase "has an inhibitory concentration of at least 1  $\mu\text{g}/\text{ml}$ " is ambiguous because it is unclear if the inhibitory concentration is less than or equal to 1  $\mu\text{g}/\text{ml}$ , if the

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inhibitory concentration is greater than or equal to 1 µg/ml, or if some inhibition is present at 1 µg/ml with inhibition occurring at concentrations above and below 1 µg/ml.

The metes and bounds are not clearly set forth.

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***Conclusion***

No claims are allowable.

ANY INQUIRY CONCERNING THIS COMMUNICATION OR EARLIER COMMUNICATIONS FROM THE EXAMINER SHOULD BE DIRECTED TO DAVID S. ROMEO WHOSE TELEPHONE NUMBER IS (571) 272-0890. THE EXAMINER CAN NORMALLY BE REACHED ON MONDAY THROUGH FRIDAY FROM 7:30 A.M. TO 4:00 P.M. IF ATTEMPTS TO REACH THE EXAMINER BY TELEPHONE ARE UNSUCCESSFUL, THE EXAMINER'S SUPERVISOR, GARY KUNZ, CAN BE REACHED ON (571) 272-0887.

IF SUBMITTING OFFICIAL CORRESPONDENCE BY FAX, APPLICANTS ARE ENCOURAGED TO SUBMIT OFFICIAL CORRESPONDENCE TO THE FOLLOWING TC 1600 BEFORE AND AFTER FINAL RIGHTFAX NUMBERS:

BEFORE FINAL (703) 872-9306

AFTER FINAL (703) 872-9307

CUSTOMERS ARE ALSO ADVISED TO USE CERTIFICATE OF FACSIMILE PROCEDURES WHEN SUBMITTING A REPLY TO A NON-FINAL OR FINAL OFFICE ACTION BY FACSIMILE (SEE 37 CFR 1.6 AND 1.8).

FAXED DRAFT OR INFORMAL COMMUNICATIONS SHOULD BE DIRECTED TO THE EXAMINER AT (571) 273-0890.

ANY INQUIRY OF A GENERAL NATURE OR RELATING TO THE STATUS OF THIS APPLICATION OR PROCEEDING SHOULD BE DIRECTED TO THE GROUP RECEPTIONIST WHOSE TELEPHONE NUMBER IS (703) 308-0196.

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DSR  
MARCH 4, 2004

  
DAVID ROMEO  
PRIMARY EXAMINER  
ART UNIT 1647

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